Remarks

Rejection under 35 U.S.C. § 112, second paragraph

Claim 44 was rejected under 35 U.S.C. § 112, second paragraph as indefinite. This rejection is respectfully traversed if applied to the amended claim.

Although it is believed the scope of claim 44 was perfectly clear to one of ordinary skill in the art, the claim has been amended so that it is perfectly clear that the variables of the seed are used for identification and differentiation of the spacers from the seeds. One skilled in the art would understand this claim.

See also the specification which states at para 0125, "In one preferred embodiment, the spacer and seed are indistinguishably linked such that no seams, welds, or joints are visible. In another embodiment, the spacer may be of a different color, texture, diameter, hardness, or shape for easy identification and demarcation." The specification goes on to state that "the spacer may be indented or otherwise marked somewhere along its length" in order to cut a chain at a place other than at the location of a seed. FIG. 3A at 20 [support at para 1010] depicts exemplary markings on spacers to facilitate their identification and demarcation from adjacent seeds in a strand. The spacers can be any color, texture, etc, or different colors, textures, etc, so long as they can be differentiated from the seeds.

Rejection Under 35 U.S.C. § 103

Claims 36-55 were rejected under 35 U.S.C. § 103 as obvious over U.S. Publication No. 2001/0044567 to Zamora *et al.* ("Zamora") in combination with U.S. Patent No. 6,010,446 to Grimm ("Grimm") and U.S. Patent No. 5,713,828 to Coniglione ("Coniglione"). This rejection is respectfully traversed.

The Claimed Invention

Claim 36 defines a brachytherapy seed

A seed, for implantation into a subject, wherein the seed is a combination product comprising

a) a biocompatible carrier,

b) one or more therapeutic components,

c) an imaging, radiopaque, or other diagnostic marker, and

d) one or more means to maintain location or orientation of the seed upon implantation selected from the group consisting of one or more biodegradable structures effective to prevent migration upon implantation of the seed into a target tissue, one or more biodegradable structures effective to maintain orientation in tissue upon implantation, and one or more compliant setal structures which impart adhesive properties upon implantation into a target tissue,

wherein the seed has a size and shape suitable for passing through the bore of a needle or catheter having an interior diameter of less than about 2.7 mm (10 gauge).

Claim 36 is novel and non-obvious over the cited art as discussed below. To make even clearer the distinction from Coniglione, however, the claim has been amended to recite that the means to maintain location or orientation are present at the time of implantation (i.e., present as part of the seed at the time of implantation). In contrast, Coniglione describes using latter occurring tissue growth to maintain the brachytherapy seeds at the site of implantation. Support is found at page 35, for example, referring to the presence of structures to secure the seeds at the time of implantation.

The Prior Art Fails to Disclose all of the Claimed Elements

None of Zamora or Grimm or Coniglione disclose

d) one or more means to maintain location or orientation of the seed selected from the group consisting of one or more biodegradable structures effective to prevent migration upon implantation of the seed into a target tissue, one or more biodegradable structures effective to maintain orientation in tissue upon implantation, and one or more compliant setal structures which impart adhesive properties upon implantation into a target tissue,

wherein the seed has a size and shape suitable for passing through the bore of a needle or catheter having an interior diameter of less than about 2.7 mm (10 gauge).

It is well established that 35 U.S.C. §103 requires a showing in the prior art of each claimed element, at a minimum, to create a *prima facie* case of obviousness.

The examiner has relied upon the statement in Zamora at paragraphs 29 and 31 referring to "the outer surface of device have sufficient permanence or persistence so that the radioactive source material remains localized at the site of implantation" for disclosure of means for maintaining the location or orientation of the seed. This reliance is misplaced.

"Persistence" and "permanence" are not the same as means for maintaining location or orientation of the seed. These terms are clearly used in reference to maintaining the integrity of the seed for a sufficient period of time for release to occur at the site where the seed is implanted. There is no disclosure of any *structure* attached to the seed to maintain its location. Persistence is defined as (1) the act or fact of persisting, (2) the quality of being persistent, (3) continued existence or occurrence, or (4) the

continuance of an effect after its cause is removed. Permanence is defined as the condition or quality of being permanent; perpetual or continued existence.

This can in no way be construed as means for maintaining a location as claimed. The other references do not make up for this deficiency. Neither discloses, nor has the examiner cited, any support in either of Grimm or Coniglione for means to maintain the seed at the desired location.

The Examiner has acknowledged that Zamora and Grimm fail to disclose biodegradable structures to prevent migration or impart adhesive properties.

Coniglione discloses a hollow-tube shape of the brachytherapy seed, allegedly to minimize the chance of migration due to better attachment to tissue [abstract]. At Col 5 lines 48-54, the specification states that this design "permits the growth of tissue into the device. This tissue growth acts to anchor the device at the application site and minimize the potential for migration."

This is *not* a means to prevent migration. This is a means to allow tissue growth, which then prevents migration. Not only is this clearly distinct from the claimed subject matter, but it attempts to solve a long standing problem (migration of brachytherapy seeds) using a totally different approach. Unfortunately, the approach is a long term, commercially unusable solution to the problem.

- *Instantaneous tissue ingrowth is biologically implausible*

Seed stabilization must occur instantly upon implantation because needle retraction is in large part responsible for dragging the seeds backwards down the needle track owing to suction. Instantaneous tissue ingrowth is biologically implausible and is not a realistic factor in prevention of seed migration.

• *Brachytherapy is used to prevent the regrowth of tissue*

Even if tissue ingrowth were important in preventing the migration of hollow-tube-shaped seeds, Conglione accurately teaches in the specification at Col 1, line 31 that brachytherapy is used "*to prevent the regrowth of tissue.*" He further recites the obvious at Col 4 line 46; Col 8 line 23; and Col 12 line 31, that radioactive implants are meant to kill tissue. In view of these teachings, tissue ingrowth cannot reasonably be expected to factor into prevention of seed migration, even if the need for seed fixity were not instantaneous.

• *Even if a seed were not radioactive, one would not expect tissue ingrowth to occur*

In "Changes in the Tumor Microenvironment During Low-dose-rate Permanent Seed Implantation Iodine-125 Brachytherapy," Cron *et al* (IJROBP 63:4; 1245-51, 2005) described local tissue changes following implantation of both inactive and radioactive I-125 brachytherapy seeds. The seeds were manufactured by IBt (aka International Brachytherapy) Inc., Conglione's employer and the assignee of U.S. Patent No. 5,713,828. Fig. 7, page 1249, depicts a "kill zone" around both the inactive and radioactive seed implant regions at two days post implant. While no explanation for this phenomenon of non-radioactive seeds killing tissue is given, we learn that even if a seed were not radioactive, one would not expect tissue ingrowth to occur. [support for IBt supplying the seeds is found at page 1246, Materials & Methods, 3rd para]

• *Hollow-tube-shape seeds migrate*

In "Prostate Postbrachytherapy Seed Distribution," Bloch *et al* (IJROBP 69:1; 70-78, 2007) describe using MRI and CT imaging to locate and quantify the extent of

dislocated (page 76, 2nd para on right) and ectopic (page 76, top right para), *i.e.* migrated, hollow-tube-shape seeds from IBt. Page 71, Materials & Methods, para 1 states that Pd-103 seeds from IBt were assessed in the study. Migrated seeds were defined as those identified beyond the prostate, or "extraprostatic/periprostatic." Table 2, page 72, shows that 11.8±4.5% of 1,205 implanted seeds were identified as having migrated to an extracapsular location. "The seeds were assigned to specific extraprostatic areas only if the dislocation was clearly visible: the seed was required to be completely extracapsular" (page 72, top right para). These findings prove that roughly 12% of hollow-tube-shape seeds migrate to outside of the prostate. Many more seeds would be expected to migrate to a lesser extent, remaining within the prostate but degrading the dosimetry outcome nonetheless. See for example the authors' comment on page 77, 3rd para left, where they state that it is often difficult to accurately determine the number of seeds implanted *"when these clump together."* Clumping occurs as a result of seed migration.

Moreover, Zamora's abstract does not describe a degradable radiopaque marker. The reference at page 4 para 0051 is to platinum, tantalum, and bismuth, which are *not* biodegradable radiopaque markers, but rather high Z elements that, by definition, cannot be further metabolized or broken down.

Evidence of Secondary Indicia of Non-obviousness

Even if the examiner had found separate references identifying the claimed elements, applicant has evidence of the type deemed by the U.S. Supreme Court sufficient to rebut an allegation of obviousness: long standing need and commercial success.

Long Standing Need

The problem with migration is a significant, and to date, unsolved problem in the field. See any of the following references.

In "A Case of Strand Migration after Prostate Seed Implant," Chuba *et al* (Poster, ESTRO 2006) demonstrated that "both individual seeds and entire strands may migrate when using strand technique."

In "Comparison of Day 0 and Day 14 Dosimetry for Permanent Prostate Implants Using Stranded Seeds," McLaughlin *et al* (IJROBP 64:1; 144-50, 2006) noted that in their study of 28 patients, "The findings of this study have clearly demonstrated a substantial change in seed position relative to the prostate and independent of prostate volume changes" (page 149, last para left). "The most common pattern was a shift of the prostate superiorly relative to the seeds, resulting in decreased prostate coverage." (page 148, 3rd para left).

In "PSA Recurrence after Brachytherapy for Seed Misplacement," Gacci *et al* (Prostate Cancer Prostatic Dis 2007 Oct, 1-3) reported that strand migration from a portion of a patient's prostate "was the main cause of tumor relapse in this area" (page 2, 1st para right)." "...In the present case, PSA recurrence occurred for seeds misplacement after a correct primary seeds positioning [*sic*]." (page 3, top left).

In "Evaluation of Source Displacement and Dose-volume Changes after Permanent Prostate Brachytherapy with Stranded Seeds," Pinkawa *et al* (Radiother Oncol 84; 190-6, 2007) found that "apparently, longer strands are moving more easily along the

prior needle track, while single seeds or shorter strands are more likely to tilt in the prostate." (page 194, top right para).

Mick Applicator users comprise about half the population of clinicians doing brachytherapy. *See* "Migration of Implanted Free Radioactive Seeds for Adenocarcinoma of the Prostate Using a Mick Applicator," Kunos *et al*, Brachytherapy 3; 71-77, 2004. Kunos describes seed migration occurring in 42% of patients (page 72, last para right).

Commercial Success

The attached materials relate to the recent introduction of brachytherapy seeds that have means for maintaining their location. This evidence, not supported by an expensive ad campaign or big name speakers, merely by the long felt need for such devices and the success immediately observed by those in the field, overwhelming demonstrates the non-obviousness of the claimed subject matter.

Summary

The claimed seeds are novel and non-obvious. The advance provided by the means for securing the seeds solves a long standing problem and has been recognized by the industry in an immediate and significant manner as providing such a solution. The claimed seeds offer a means of enhancing seed and strand fixity such that implant dosimetry is improved, irrespective of the implant technique. It also may eliminate the logistical nightmare entailed in stranding your own seeds.

Double Patenting Rejection

Claims 36-40, 45, and 47-55 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 5, 10, 12, 15, 30, 32, 35, and 36 of U.S. Patent No. 6,746,661 to Kaplan. This rejection is traversed.

The mere fact that claims are drawn to brachytherapy seeds, formed of a biodegradable polymer, but having distinct limitations - one drawn to elastic properties of the polymer and the other to distinct structures for maintaining the location of the seed, does not make them obvious over the other. If they had appeared in the same application, the examiner would have issued a restriction requirement on the grounds that they required different searches, in different arts. Elastic polymers do not make obvious means for maintaining seeds in a particular location. Accordingly, claims 36-40, 45, and 47-55 are not obvious over the claims in U.S. Patent No. 6,747,661 to Kaplan, et al.

Allowance of new claims 36-55 is respectfully solicited. **Should there be any remaining issues the undersigned requests an interview with the examiner, his supervisor and a quality control specialist to resolve these issues.**

Respectfully submitted,

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